

**Amendments to the Specification:**

Please add the following new paragraph after the title of the application beginning at page 1, line 1:

**Cross-Reference to Related Applications**

-- This applications is a divisional of application Serial No. 09/428,082, filed October 22, 1999, which claims the benefit of United States Provisional application 60/105,371, filed October 23, 1998, which are incorporated by reference herein. --

Please replace the following paragraphs and table with the following rewritten paragraphs and table:

At page 13, lines 16-19:

Figure 5 shows a synthetic scheme for the preparation of PEGylated peptide 19 (SEQ ID NO: 3) as prepared through intermediates having SEQ ID NOS: 1128 through 1131, respectively.

Figure 6 shows a synthetic scheme for the preparation of PEGylated peptide 20 (SEQ ID NO: 4) as prepared through intermediates having SEQ ID NOS: 1132 and 1133, respectively.

At page 16, lines 23-25:

Figures 23A, ~~23B~~, and ~~23C~~ and 23B show the nucleotide and amino acid sequences (SEQ ID NOS: 1063 and 1064) of the Fc-VEGF antagonist fusion molecule described in Example 6 hereinafter.

At page 58, Table 20:

**Table 20—Additional Exemplary Pharmacologically Active Peptides**

| Sequence/structure   | SEQ ID NO:             | Activity         |
|----------------------|------------------------|------------------|
| VEPNCDIHVMWEWECFERL  | 1027                   | VEGF-antagonist  |
| GERWCDFDGPLTWVCGEES  | <del>1084</del><br>398 | VEGF-antagonist  |
| RGWVEICVADDNGMCVTEAQ | 1085                   | VEGF-antagonist  |
| GWDECDVARMWEWECFAGV  | 1086                   | VEGF- antagonist |
| GERWCDFDGPRAWVCGWEI  | 501                    | VEGF- antagonist |
| EELWCDFDGPRAWVCGYVK  | 502                    | VEGF- antagonist |
| RGWVEICAADDYGRCLTEAQ | 1031                   | VEGF- antagonist |
| RGWVEICESDVWGRCL     | 1087                   | VEGF- antagonist |
| RGWVEICESDVWGRCL     | 1088                   | VEGF- antagonist |
| GGNECDIARMWEWECFERL  | 1089                   | VEGF- antagonist |
| RGWVEICAADDYGRCL     | 1090                   | VEGF-antagonist  |

|   |      |   |
|---|------|---|
| CTTHWGFTLC  | 1028 | MMP inhibitor                           |
| CLRSGXGC  | 1091 | MMP inhibitor                           |
| CXXHWGFXXC  | 1092 | MMP inhibitor                           |
| CXPXC   | 1093 | MMP inhibitor                           |
| CRRHWGFEC   | 1094 | MMP inhibitor                           |
| STTHWGFTLS  | 1095 | MMP inhibitor                           |
| CSLHWGFWWC  | 1096 | CTLA4-mimetic                           |
| GFVCSGIFAVGVGRC   | 125  | CTLA4-mimetic                           |
| APGVRLGCAVLGRYC   | 126  | CTLA4-mimetic                           |
| LLGRMK  | 105  | Antiviral (HBV)                         |
| ICVVQDWGHHRCTAGHMANLTSHASAI   | 127  | C3b antagonist                          |
| ICVVQDWGHHRCT   | 128  | C3b antagonist                          |
| CVVQDWGHHAC   | 129  | C3b antagonist                          |
| STGGFDDVYDWARGVSSALTTTLVATR   | 185  | Vinculin-binding                        |
| STGGFDDVYDWARRVSSALTTTLVATR   | 186  | Vinculin-binding                        |
| SRGVNFSEWLYDMSAAMKEASNVFPSRRSR  | 187  | Vinculin-binding                        |
| SSQNWDMEAGVEDLTAAMLGLLSTIHSSSR  | 188  | Vinculin-binding                        |
| SSPSLYTQFLVNYESAATRIQDLLIASRPSR   | 189  | Vinculin-binding                        |
| SSTGWVDLLGALQRAADATRTSIPPSLQNSR   | 190  | Vinculin-binding                        |
| DVYTKKELIECARRVSEK  | 191  | Vinculin-binding                        |
| EKGSYYPGSGIAQFHIDYNNVS  | 192  | C4BP-binding                            |
| SGIAQFHIDYNNVSSAEGWHVN  | 193  | C4BP-binding                            |
| LVTVEKGSYYPGSGIAQFHIDYNNVSSAEGWHVN  | 194  | C4BP-binding                            |
| SGIAQFHIDYNNVS  | 195  | C4BP-binding                            |
| LLGRMK  | 279  | anti-HBV                                |
| ALLGRMKG  | 280  | anti-HBV                                |
| LDPAFR  | 281  | anti-HBV                                |
| CXXRGDC   | 322  | Inhibition of platelet aggregation      |
| RPLPPLP   | 323  | Src antagonist                          |
| PPVPPR  | 324  | Src antagonist                          |
| XFDXWXXLXX  | 325  | Anti-cancer (particularly for sarcomas) |
| KACRRLFGPVDSEQLSRDCD  | 326  | p16-mimetic                             |
| RERWNFDVFTETPLEGDFAW  | 327  | p16-mimetic                             |
| KRRQTSMTDFYHSKRRLIFS  | 328  | p16-mimetic                             |
| TSMTDFYHSKRRLIFSKRKP  | 329  | p16-mimetic                             |
| RRLIF   | 330  | p16-mimetic                             |
| KRRQTSATDFYHSKRRLIFSRQIKIWFQNRRMKWKK  | 331  | p16-mimetic                             |
| KRRLIFSKRQIKIWFQNRRMKWKK  | 332  | p16-mimetic                             |
| Asn Gln Gly Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe Val Met Thr Ala Ala Ser Cys Phe Gln         | 498  | CAP37 mimetic/LPS binding               |
| Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe Val Met Thr Ala Ala Ser Cys                             | 499  | CAP37 mimetic/LPS binding               |
| Gly Thr Arg Cys Gln Val Ala Gly Trp Gly Ser Gln Arg Ser Gly Gly Arg Leu Ser Arg Phe Pro Arg Phe Val Asn Val | 500  | CAP37 mimetic/LPS binding               |
| WHWRHRIPLQLAAGR   | 1097 | carbohydrate (GD1 alpha) mimetic        |
| LKTPRV  | 1098 | β2GPI Ab binding                        |

|                             |      |                         |
|-----------------------------|------|-------------------------|
| NLTKTDRV                    | 1099 | $\beta$ 2GPI Ab binding |
| NLTKTDRVGGC                 | 1100 | $\beta$ 2GPI Ab binding |
| KDKATF                      | 1101 | $\beta$ 2GPI Ab binding |
| KDKATFGCHD                  | 1102 | $\beta$ 2GPI Ab binding |
| KDKATFGCHDGC                | 1103 | $\beta$ 2GPI Ab binding |
| TLRVYK                      | 1104 | $\beta$ 2GPI Ab binding |
| ATLRVYKGG                   | 1105 | $\beta$ 2GPI Ab binding |
| CATLRVYKGG                  | 1106 | $\beta$ 2GPI Ab binding |
| INLKALAALAKKIL              | 1107 | Membrane-transporting   |
| GWT                         | NR   | Membrane-transporting   |
| GWTLNSAGYLLG                | 1108 | Membrane-transporting   |
| GWTLNSAGYLLGKINLKALAALAKKIL | 1109 | Membrane-transporting   |

At page 109, lines 3-15:

The Fc portion of the molecule was generated in a PCR reaction with pFc-A3 using the primers

1216-52      AAC ATA AGT ACC TGT AGG ATC G

1798-17      AGA GTA AGT ACC TCC ACC ACC ACC TCC ACC TTT ACC CGG  
AGA CAG GGA GAG GCT CTT CTG C

which are SEQ ID NOS: ~~398~~369 and 399, respectively. The oligonucleotides 1798-17 and 1798-18 contain an overlap of 61 nucleotides, allowing the two genes to be fused together in the correct reading frame by combining the above PCR products in a third reaction using the outside primers, 1216-52 and 1798-19.

At page 113, lines 22-23:

The nucleotide and amino acid sequences (SEQ ID NOS: 21 and 22, respectively) of the fusion protein are shown in Figure 16.

At page 114, lines 20-30 and page 115, lines 1-5:

Fc-TNF- $\alpha$  inhibitors. A DNA sequence coding for the Fc region of human IgG1 fused in-frame to a monomer of the TNF- $\alpha$  inhibitory peptide was constructed using standard PCR technology. The Fc and 5 glycine linker portion of the molecule was generated in a PCR reaction with DNA from the Fc-EMP fusion strain #3718 (see Example 3) using the sense primer 1216-52 and the antisense primer 2295-89 (SEQ ID NOS:

~~1112369~~ and ~~11131112~~ , respectively). The nucleotides encoding the TNF- $\alpha$  inhibitory peptide were provided by the PCR primer 2295-89 shown below:

1216-52        AAC ATA AGT ACC TGT AGG ATC G

2295-89        CCG CGG ATC CAT TAC GGA CGG TGA CCC AGA GAG GTG TTT TTG TAG  
                  TGC GGC AGG AAG TCA CCA CCA CCT CCA CCT TTA CCC

The oligonucleotide 2295-89 overlaps the glycine linker and Fc portion of the template by 22 nucleotides, with the PCR resulting in the two genes being fused together in the correct reading frame.

At page 117, lines 21-30 and page 118, lines 1-8:

Fc-IL-1 antagonist. A DNA sequence coding for the Fc region of human IgG1 fused in-frame to a monomer of an IL-1 antagonist peptide was constructed using standard PCR technology. The Fc and 5 glycine linker portion of the molecule was generated in a PCR reaction with DNA from the Fc-EMP fusion strain #3718 (see Example 3) using the sense primer 1216-52 and the antisense primer 2269-70 (SEQ ID NOS: ~~1112369~~ and 1118, respectively). The nucleotides encoding the IL-1 antagonist peptide were provided by the PCR primer 2269-70 shown below:

1216-52        AAC ATA AGT ACC TGT AGG ATC G

2269-70        CCG CGG ATC CAT TAC AGC GGC AGA GCG TAC GGC TGC CAG TAA CCC GGG GTC  
                  CAT TCG AAA CCA CCA CCT CCA CCT TTA CCC

The oligonucleotide 2269-70 overlaps the glycine linker and Fc portion of the template by 22 nucleotides, with the PCR resulting in the two genes being fused together in the correct reading frame.

At page 121, lines 4-15:

Fc-VEGF Antagonist. A DNA sequence coding for the Fc region of human IgG1 fused in-frame to a monomer of the VEGF mimetic peptide was constructed using standard PCR technology. The templates for the PCR reaction were the pFc-A3 plasmid and a synthetic VEGF mimetic peptide gene. The synthetic gene was assembled by annealing the following two oligonucleotides primer (SEQ ID NOS: ~~11201110~~ and ~~11211111~~, respectively):

2293-11        GTT GAA CCG AAC TGT GAC ATC CAT GTT ATG TGG GAA TGG GAA  
                  TGT TTT GAA CGT CTG

2293-12        CAG ACG TTC AAA ACA TTC CCA TTC CCA CAT AAC ATG GAT GTC  
                  ACA GTT CGG TTC AAC

At page 121, lines 17-18:

The two oligonucleotides anneal to form the following duplex encoding an amino acid sequence shown below (SEQ ID NOS: ~~1122~~1113 and 1114):

At page 121, lines 28-29:

This duplex was amplified in a PCR reaction using 2293-05 and 2293-06 as the sense and antisense primers (SEQ ID NOS: ~~1125~~1122 and ~~1126~~1123).

At page 121, lines 30-34:

The Fc portion of the molecule was generated in a PCR reaction with the pFc-A3 plasmid using the primers 2293-03 and 2293-04 as the sense and antisense primers (SEQ ID NOS: ~~1123~~1120 and ~~1124~~1121, respectively). The full length fusion gene was obtained from a third PCR reaction using the outside primers 2293-03 and 2293-06. These primers are shown below:

At page 122, lines 22-31:

VEGF antagonist -Fc. A DNA sequence coding for a VEGF mimetic peptide fused in-frame to the Fc region of human IgG1 was constructed using standard PCR technology. The templates for the PCR reaction were the pFc-A3 plasmid and the synthetic VEGF mimetic peptide gene described above. The synthetic duplex was amplified in a PCR reaction using 2293-07 and 2293-08 as the sense and antisense primers (SEQ ID NOS: ~~1127~~1124 and ~~1128~~1125, respectively).

The Fc portion of the molecule was generated in a PCR reaction with the pFc-A3 plasmid using the primers 2293-09 and 2293-10 as the sense and antisense primers (SEQ ID NOS: ~~1129~~1126 and ~~1130~~1127, respectively).

At page 123, lines 27-32 and page 124, lines 1-22:

Fc-MMP inhibitor. A DNA sequence coding for the Fc region of human IgG1 fused in-frame to a monomer of an MMP inhibitory peptide was constructed using standard PCR technology. The Fc and 5 glycine linker portion of the molecule was generated in a PCR reaction with DNA from the Fc-TNF- $\alpha$  inhibitor fusion strain #4544 (see Example 4) using the sense primer 1216-52 and the antisense primer 2308-67 (SEQ ID NOS: ~~1112~~1369 and ~~1113~~1115, respectively). The nucleotides encoding the MMP inhibitor peptide were provided by the PCR primer 2308-67 shown below:

1216-52            AAC ATA AGT ACC TGT AGG ATC G

2308-67            CCG CGG ATC CAT TAG CAC AGG GTG AAA CCC CAG TGG GTG GTG  
                      CAA CCA CCA CCT CCA CCT TTA CCC

The oligonucleotide 2308-67 overlaps the glycine linker and Fc portion of the template by 22 nucleotides, with the PCR resulting in the two genes being fused together in the correct reading frame.

At page 124, lines 22-35:

MMP Inhibitor-Fc. A DNA sequence coding for an MMP inhibitory peptide fused in-frame to the Fc region of human IgG1 was constructed using standard PCR technology. The Fc and 5 glycine linker portion of the molecule was generated in a PCR reaction with DNA from the Fc-TNF- $\alpha$  inhibitor fusion strain #4543 (see Example 4). The nucleotides encoding the MMP inhibitory peptide were provided by the sense PCR primer 2308-66, with primer 1200-54 serving as the antisense primer (SEQ ID NOS: ~~4132~~1116 and 407, respectively).

The primer sequences are shown below:

|         |  |
|---------|--|
| 2308-66 | GAA TAA CAT ATG TGC ACC ACC CAC TGG GGT TTC ACC CTG TGC<br>GGT GGA GGC GGT GGG GAC AAA |
| 1200-54 | GTT ATT GCT CAG CGG TGG CA   |

The two oligonucleotides anneal to form the following duplex encoding an amino acid sequence shown below (SEQ ID NOS: 1113 and 1114 ):